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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Vern Maine & Associates
100 MAIN STREET
P O BOX 3445
NASHUA, NH 03061-3445

EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/515,984	COESTER, CARL-FR	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-42* is/are pending in the application.

4a) Of the above claim(s) *40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/18/08*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to the amendment submitted on 08/18/08. Claims 32-42 are currently pending in the application, with claims 1-31 having being cancelled and claim 40-42 having being withdrawn. Accordingly, claims 32-39 are being examined on the merits herein.

Applicant's argument that the Examiner has not established a prima facie case of obviousness and that in fact the Examiner utilized hindsight reconstruction has been fully considered but is not found persuasive. The use of three references was utilized and which rendered the instant invention obvious. Cutson discusses the cardinal signs of Parkinson disease and teaches the use of L-Dopa as the mainstay therapy. Moreover, Cutson further discusses the use of combinatorial therapy entailing L-dopa since large amount of L-Dopa alone tends to lead to adverse affects. However, Cutson teaches that the effects of dopamine agonists are mostly focus on the rigidity symptoms. Silvestrini teaches the use of trazodone and etoperidone in treating tremors associated in Parkinson disease. Importantly, Silvestrini reiterates the problems associated with dopamine agonists that mostly target rigidity and not the tremor symptoms associated with such disease. Conversely, Kent was provided to demonstrate that nefazodone was developed to improve the pharmacological

characteristics of trazodone and suggests the effective dosage of nefazodone. Thus, in view of the teachings of Cutson, Silvestrini, and Kent, one of ordinary skill in the art would have found it obvious to substitute nefazodone for trazodone and combine L-Dopa with nefazodone since each compound will target each main component of Parkinson disease. Thus, the motivation to modify the references lies in the improved characteristics of nefazodone over trazodone and the fact that L-Dopa addresses the problem with rigidity as taught by Cutson and Silvestrini and that trazodone affects the tremors associated with Parkinson disease. As for applicant's argument that nefazodone was not known for the treatment of Parkinson disease, such arguments are not persuasive as Silvestrini clearly teaches the use of trazodone to address the problems of tremors associated with Parkinson disease. Furthermore, in view of KSR, one of ordinary skill would have found it obvious to try nefazodone in the combination therapy since Silvestrini (published in 1979, well ahead of the invention) clearly suggests the use of trazodone in addressing the symptoms of tremors associated with Parkinson disease and given that Kent teaches nefazodone as an improvement over trazodone. In light of the aforementioned disclosures, the Examiner contends that Cutson in view of Silvestrini and in further view of Kent do indeed render obvious applicant's invention and thus the rejection of record is maintained.

Applicant's contention that Silvestrini conducted his test based on a nicotinic induced tremors and that the lack of conclusive data compounded by the fact that Albanese published in 1988 shows a deterioration of Parkinson disease or the

anecdotal letter of Bernazzi has been fully considered but is not found persuasive. While Albanese questions the involvement of trazodone in 1 patient or the fact that Bernazzi stated that the one patient report (not tested but observed) might be due to this patient's sensitivity to SSRI, Silvestrini clearly showed that trazodone was effective in inhibiting tremors in 10 out of 13 patients (i.e. 76%) regardless of its source (see Silvestrini, col. 5, lines 52-61). In fact, Silvestrini's clinical results demonstrate the potential pleiotropic tremor effects of trazodone. Thus, in light of Kent who teaches nefazodone as an improvement of trazodone and in light of the teachings of Silvestrini, it would have been obvious to one of ordinary skill in the art to at least try nefazodone to treat the tremors of Parkinson disease. Once again, the Examiner contends that one of ordinary skill in the art would not have been deterred from utilizing nefazodone to treat Parkinson disease. As a result, the Examiner maintains the rejection of record.

Applicant's argument with respect to the fact that the instant invention provides a long-felt need in the treatment of Parkinson Disease has again been fully considered but is not found persuasive. While long-felt need along with the failure of others to successfully treat Parkinson disease can show unobviousness, the Examiner asserts that there is no evidence of any prior unsuccessful attempts since L-Dopa is the mainstay therapy and the fact that Silvestrini has suggested the use of triazolopyridine derivatives as effective against tremors, this suggests that such long-felt need has been satisfied by the teachings of Cutson in view of Silvestrini and in further view of Kent.

For the foregoing reasons, the rejection of claims 32-39 under 103 (a) remains proper and is maintained. For applicant's convenience, the 103 (a) Final rejection is re-stated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-38 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Cutson et al. (Physical Therapy, 1995, Vol. 75, No.5, pgs. 363-373, previously cited) in view of Silvestrini (U.S. 4,132,791, previously cited) and in further view of Kent (The Lancet, 2000, Vol. 355, pgs. 911-918, previously cited).

Cutson et al. teach that Parkinson's disease is a neurodegenerative disease characterized by cardinal signs such as tremors, bradykinesia, rigidity, and postural instability due to loss of dopamine which consequentially result in reduced excitatory motor cortex and occurrence of other symptoms including depression (see pg. 363, Introduction, left col., pg. 364, right col. last paragraph, and pg. 365, left and middle col.). Cutson et al. further teach that L-dopa is the mainstay treatment but as dopamine

does not cross the blood brain barrier, the levo-isomer (L-dopa) is typically given since it enters the central nervous system (CNS) and undergo enzymatic conversion to dopamine (see pg. 366, middle col.). However, given that L-dopa is rapidly metabolized peripherally before crossing into the brain, large amount of L-Dopa is generally necessitated; however, to avoid adverse effects with large amount of L-Dopa, the combination of carbidopa, a peripheral decarboxylase inhibitor that prevents peripheral conversion of L-dopa, with Levodopa or the composition Sinemet (i.e. tablet composition of carbidopa and levodopa; instant claim 38) is the commonly form used to date containing 50 mg of carbidopa and 200 mg of levodopa or 25 mg of carbidopa and 100 mg of levodopa (i.e. Sinemet CR) (instant claims 33-35; see L-Dopa section, pg. 366, middle col.). Importantly, Cutson et al. teach that the effects of dopamine agonists such as Amantadine are mostly on the symptom of rigidity (see pg. 368, Dopamine agonist section, left col.).

Cutson et al. do not specifically teach a method of treating Parkinson disease comprising a composition comprising 2-[3-[4[-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4,-triazol-3(4H)-one (i.e. nefazodone). Similarly, Cutson et al. do not teach a method comprising administered said composition in two to three single doses or in one or more single doses of about 100 mg to about 200 mg.

Silvestrini teaches treatment of tremors in Parkinsonism by administering trazodone and etoperidone in the range of 25 mg to 100 mg three times a day (see

abstract). Silvestrini further teaches that Parkinson disease is characterized by tremors and muscular hypertonia, and administration of the psychotropic agents, trazodone and etoperidone, will reduce the two main components of Parkinson's disease (see col. 1, lines 10-62). Moreover, Silvestrini teaches that dopaminergic or adrenergic compounds, such as L-Dopa or dopamine agonists such as Amantadine, are mostly effective against rigidity and in fact may produce tremors and side effects and therefore suggest that tremors and rigidity have a different neurotransmitter basis (see col. 2, lines 25-30). Silvestrini demonstrated that adrenergic substances such as clonitidine induce tremors and are inhibited by trazodone and etoperidone (see col. 2, lines 31-56). Likewise, Silvestrini demonstrated that trazodone or etoperidone pre-administration followed by nicotine administration abrogated nicotine-induced tremors (see col. 3, lines 4-7). Since trazodone and etoperidone have potent adrenolytic action, Silvestrini concluded that the anti-tremor activity of trazodone and etoperidone are due to the fact that they are adrenolytic agents (see col. 4, lines 50-58 and col. 4, table II). Additionally, Silvestrini teaches that the dosage of trazodone employed in various studies was 50 mg capsule three times daily (instant claims 36-37; see col. 5, lines 1-5).

Kent teaches new antidepressant with greater specificity including nefazodone (see abstract, pg. 911). Importantly, Kent teaches that nefazodone is structurally related to trazodone (see pg. 912, left col. paragraph 1). Moreover, Kent teaches that nefazodone was developed to improve the pharmacological characteristics of the earlier antidepressant trazodone (see pg. 912, right col. paragraph 1). Moreover, the

recommended doses of nefazodone is 200 mg per day (i.e. single dose) or 100 mg twice a day (i.e. multiple single dose) wherein the dose can range from 300-600 mg daily (see pg. 912, right col. paragraph 2).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to substitute nefazodone into the composition of Silvestrini since trazodone and nefazodone are functional equivalents and are structurally similar. Moreover, it is considered that one of ordinary skill in the art at the time of the invention was made would have found it obvious to substitute the nefazodone of Kent for the trazodone of Silvestrini given that the substitution of one known element for another would have yielded predictable results.

Additionally, one of ordinary skill in the art at the time of the invention would have bound it obvious to combine the now modified composition of Silvestrini with the composition of Cutson et al. since Silvestrini teaches that L-Dopa is mostly effective against rigidity and not tremor symptoms. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Thus, given that Cutson et al. teach a method of treating Parkinson disease with L-Dopa, and Silvestrini teaches that L-Dopa is not effective against rigidity and suggests

the use of trazodone and/or etoperidone for anti-tremor activity, and Kent teaches that nefazodone is structurally similar to trazodone and was developed to improve over the adverse effects of trazodone, one of ordinary skill would have been motivated to substitute nefazodone for trazodone as taught by Kent, and combine the methods of Silvestrini and Cutson et al. with the reasonable expectation of providing a successful method of treating Parkinson disease that is efficacious in alleviating rigidity and efficacious in suppressing tremors.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cutson et al. (Physical Therapy, 1995, Vol. 75, No.5, pgs. 363-373, previously cited) in view of Silvestrini (U.S. 4,132,791) and in further view of Kent (The Lancet, 2000, Vol. 355, pgs. 911-918, previously cited) as applied to claims 32-38 above and in further view of Ross et al. (JAMA. 2000, Vol. 283, No. 20, pgs. 2674-2679, previously cited).

The Cutson, Silvestrini and Kent references are as discussed above and incorporated by reference herein. However, Cutson, Silvestrini and Kent do not address the addition of caffeine or acetyl salicylic acid or combinations thereof in the aforementioned method of treatment.

Ross et al. teach that no treatment exist to slow the progression of Parkinson Disease (see pg. 2674, left col. paragraph 1). Ross et al. further teach that coffee intake has been inversely associated with PD occurrence but found that PD incidence decline consistently with increased amount of caffeine intake (instant claim 39; see abstract-Results, fig. 1, table 2, and figure 2). This reduction in incidence is taught by Ross et al. to be due to possibly caffeine being neuroprotective or counteracting aging related neurodegeneration, or the antagonistic effect of caffeine on adenosine A2 receptors which improves motor deficits as seen in animals, or the fact that caffeine can decrease clinical expression of Parkinsonism by increasing dopaminergic tone (see pg. 2678, middle col.).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to add caffeine into the method of Cutson and Silvestrini since Ross et al. teaches that caffeine may play a role in slowing aging-induced neurodegeneration. Given that Cutson et al. teach a method of treating Parkinson disease with L-Dopa, and Silvestrini teaches that L-Dopa is not effective against rigidity and suggests the use of trazodone and/or etoperidone for anti-tremor activity, and Kent teaches that nefazodone is structurally similar to trazodone and was developed to improve over the adverse effects of trazodone, and Ross et al. teach that caffeine may slow aging-induced neurodegeneration, one of ordinary skill would have been motivated to substitute nefazodone for trazodone as taught by Kent, and combine the methods of Silvestrini and Cutson et al. and add caffeine with the reasonable expectation of providing an enhanced method of treating Parkinson disease that is efficacious in alleviating rigidity

and tremors and a method efficient in slowing down the progression of Parkinson's disease.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

11/20/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617